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# A systemic review and meta-analysis on the impact of perioperative antiplatelets and anticoagulants on the clinical course of chronic subdural hematoma

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# **A systemic review and meta-analysis on the impact of perioperative antiplatelets and anticoagulants on the clinical course of chronic subdural hematoma**

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I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree Master of Surgery, MCh is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work.

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## **Abstract:**

**Background:** Chronic subdural hematoma is one of the most common conditions related to neurosurgical practice in the elderly. Reports about recurrence of patients on antiplatelets and/or anticoagulants are highly contradictory. Little current data exists regarding the outcome of chronic subdural hematoma patients on peri-operative medication related coagulopathy. We aimed to review the literature for studies about these drugs and outcome in chronic subdural hematoma patients.

**Objectives:** to perform a systematic review and meta-analysis of studies that examines the impact of antiplatelets and anticoagulants on the clinical evolution of chronic subdural hematoma.

**Methods:** We searched the Cochrane Library, PubMed, Scirus, MEDLINE, EMBASE, and the American Association of Neurological Surgeons (AANS) Database, and the conference proceedings of the European Association of Neurosurgical Societies (EANS). We also checked the reference lists of all retrieved studies and Controlled Trials metaRegister to identify any further studies. We searched the Internet using Google Scholar. We also contacted experts in the field as well as authors of the included studies. Searching was not restricted by date, language or publication status.

**Selection criteria:** Prospective and/or retrospective studies that examine the effect of anticoagulant and antiplatelet drugs on the clinical course of chronic subdural hematoma. **Data collection and analysis:** The author was the main data collector and investigator from the identified studies. The data needed extracted for analysis. We collected data related to the outcome of subdural hematoma and anticoagulation drugs from the included studies. Two reviewers independently checked the eligibility, study selection, methodological quality, risk of bias and



extracted data. They also independently assessed the risk of bias assessments for the included studies according to the Cochrane Handbook for Systematic Reviews of Interventions. The authors of the study were contacted for missing information when possible. We pooled results of clinically and statistically homogeneous studies, where possible, to provide estimates of the effect of antiplatelets and anticoagulants. Then, we undertook separate subgroup analyses and meta-analysis for recurrent subdural hematoma only. We also calculated the risk ratios (RR) with 95% confidence intervals (CI). Any disagreements were managed by consensus after discussion among the author, the independent reviewers and the supervisors.

**Main results:** no randomised controlled trials were identified. We included eleven clinical cohort studies involving 1854 and 365 participants for the recurrent and bilateral categories, respectively. There was a significant increase in the risk of antipalatelets, with a pooled relative risk of 1.88. However, the pooled relative risk of anticoagulants was only 1.26 and it was not statistically significant.

**Authors' conclusions:** formal recommendations can be made about the proper use and regular follow up of antiplatelets in patients. Anticoagulants do not significantly affect recurrent chronic subdural hematoma. Non-controlled studies usually come up with conflicting results. Therefore, further work is required in order to establish any potential effect of the new and old anticoagulation medications on the clinical course of chronic subdural hematoma. There is a need for well designed randomised controlled trials and prospective studies with large sample sizes and stratification of the different types of anticoagulation drugs investigating the role of antiplatelets and anticoagulants on chronic subdural hematoma.

**Keywords:** subdural hematoma/haematoma; recurrent/recurrence; anticoagulant; antiplatelet/antiaggregation; heparin; warfarin; aspirin; clopidogrel.

**Abbreviations:** CSDH: chronic subdural hematoma; CT scan: Computed tomography scan; INR: international normalized ratio; RCTs: randomised controlled trials; SDH: subdural hematoma

The use of the terms “anticoagulation” and “anticoagulant” are used differently in this review. The term anticoagulation is used as a descriptive expression for both antiplatelet and anticoagulant drugs. However, the term anticoagulant is used to describe a substance that prevents clotting of blood, such as warfarin, heparin and other similar class of pharmaceuticals.

# 1. Introduction

## 1.1 Background

Chronic subdural hematoma (CSDH) is one of the most commonly admitted conditions to the neurosurgical unit. It was first described by Wepfer in 1656. It refers to a slowly growing encapsulated collection of blood and its breakdown products between the dura mater and the arachnoids in the subdural space (1, 2). The incidence of this condition increases greatly with age, it is about 1 to 2 per 100,000 individuals per year aged over 60, while that in individuals aged over 70 is 7.4 per year (3). Virchow postulated that a pachymeningitis hemorrhagica interna was the origin of chronic subdural hematoma in 1857 (4). Half a century later, in 1914, Trotter considered the bleeding to be of traumatic and venous in origin. His theory became increasingly accepted, even for patients with inapparent trauma, and it remains the accepted cause for most patients (5). Therefore, the current literature identify the likely cause as that subdural hematomas arise from the tearing of bridging veins as a result of brain atrophy, and/or weakness of venous walls in elderly patients. Cortical bridging veins are thought to be under greater tension as the brain gradually shrinks from the skull; even minor trauma may cause one of these veins to tear. (6-8). A history of head trauma is identified in 80% of patients, and in most cases the trauma is mild (9, 10). Hematoma thickness tends to be larger in older patients due to a decrease in brain weight and increase in subdural space with age (3). In patients older than 50 years, the mass of the brain is reduced by approximately 200 g, which results in an increased extracerebral volume of up to 11%. This extra volume can be occupied by the haematoma before a considerable rise in intracranial pressure occurs. In addition, a slowly progressing haematoma allows the brain to adjust to the new situation by compressing the venous channels, thus providing further space for the haematoma to expand (10). Classically chronic subdural hematomas contains motor motor oil fluid which does not clot (11). When the subdural fluid is clear, the collection is termed a subdural hygroma (12). Clinical presentation differs widely within the patient groups, ranging from

asymptomatic to decreased cognitive functions, severe neurological deficits or even life-threatening herniation (2, 13-15). If a haematoma has formed within the subdural space, it can be maintained by anticoagulative treatment, ethylism or haematological disorders (3, 16-21). The reasons why this type of hematoma occurs frequently among the elderly include an increase in antithrombotic medications, venous fragility, augmentation of the subdural space, and an increased exposure to traumatic injury resulting from frequent falls (14).

Many chronic subdural hematomas probably start out as acute subdural. Blood within the subdural space evokes an inflammatory response. Within days, fibroblasts invade the clot, and form neomembranes on the inner (cortical) and outer (dural) surface. This is followed by ingrowths of neocapillaries, enzymatic fibrinolysis, and liquefaction of blood clot. Fibrin degradation products are reincorporated into new clots and inhibit hemostasis. The course of chronic subdural hematomas is determined by the balance of plasma effusion and / or rebleeding from the neomembranes on the one hand and reabsorption of fluid on the other (22).

Definitive diagnosis of chronic subdural hematoma relies on computed tomography (CT) imaging of the head. On a CT scan, subdural hematomas are classically crescent-shaped, with a concave surface away from the skull. However, they can have a convex appearance, especially in the early stage of bleeding. This may cause difficulty in distinguishing between subdural and epidural hemorrhages. A more reliable indicator of subdural hemorrhage is its involvement of a larger portion of the cerebral hemisphere since it can cross suture lines, unlike an epidural hemorrhage (12). Associated membranes may enhance with intravenous contrast, which can be useful in preoperative planning (23). Neurosurgeons are quite familiar with the condition and many of them consider symptomatic chronic subdural hematoma prompt specialized evaluation and neurosurgical intervention by surgical decompression often on an emergency basis. The majority of patients have good outcome after surgical treatment of chronic subdural hematoma. Following surgical treatment, 80 to 90% of the patients recover their premorbid function (24-26). Despite, complications like wound infection, subdural empyema, tension pneumocephalus, brain

contusion, catheter penetration of the brain and even death may occur after surgery (27), but recurrent subdural hematoma is the most important complication encountered that needs reoperation in the majority of patients as this increases the morbidity and mortality of the individual (28). In asymptomatic patients, or patients with relatively small hematomas conservative management with nonoperative measures, such as, hypertonic or hyperosmolar solutions and systemic glucocorticoids have been used in CSH with favourable results (22, 29, 30). Using relatively simple and safe procedures a neurosurgeon can initiate often dramatic improvement in the patient's condition. However, not all patients improve and recurrence is again a major consideration.

## **1.2 Burden of the problem**

Chronic subdural hematomas in patients treated with anticoagulant account for 5% of all CSDHs (31). According to a recent retrospective review, anticoagulants significantly increase the risk of developing chronic subdural hematoma up to 42.5 times, relative to the general population (32). In another studies, 41% (33) and 24% (34) of all chronic subdural hematoma patients admitted were anticoagulated. Compared with non-anticoagulation-related hematomas, the risk of haemorrhage was calculated to be increased fourfold in men and thirteen fold in women (34). Recurrent bleedings imply recurrence of mass effect which causes clinical symptoms, such as headaches, decreased level of consciousness as well as focal disorders, e.g. motor weakness, dysphasia or partial amnesia (7, 35, 36). This recurrence can result in reoperation with all the complications related to surgery as well as those associated with the general anaesthesia (37). There is a clinical improvement when the subdural pressure is reduced to close to zero which usually occur after approximately 20% of the collection is removed (10). Residual subdural fluid collections after treatment are common, but clinical improvement does not require complete resolution of the fluid collection on computed axial tomography. The scans showed persistent fluid in 78% of cases on post-op day 10, and in 15 % after 40 days (26), and may take up to 6 months for complete resolution. It is recommended not to treat persistent fluid collections evident on scan. Especially before 20 days post-op, unless it in-

creases in size on computed tomography or if the patient shows no recovery or deteriorates (12).

Although the majority of chronic subdural hematomas resolve following a single neurosurgical intervention, chronic subdural hematoma (CSDH) has been reported to have a substantial recurrence rate ranging from 9.2 to 26.5% (37-42). The risk factors for recurrence are thought to be the following: old age, poor performance status at admission, cerebral atrophy, large hematoma, alcohol ingestion, usage of anticoagulants, renal failure, liver dysfunction, septum formation in the hematoma, and meningeal dissemination of malignant tumor (42-45). Although several articles reported antiplatelet and anticoagulant related recurrence, others studies have not disclosed any significant results (46-49).

Bilateral subdural hematoma cases were infrequently experienced and little is known about them (50) except that they might be related to the coagulofibrinolytic abnormalities (51). Although chronic subdural hematoma is a common occurrence, data on bilateral chronic subdural hematoma are scarce compared to the studies on the unilateral ones. Bilateral chronic subdural hematoma makes up 16% to 20% of chronic subdural hematoma cases (45), especially those older than 75 years (52) and those with coagulation abnormalities (51). Furthermore, bilateral chronic subdural hematoma has been considered to be a risk factor for recurrence of chronic subdural hematoma in previous studies (45, 53). The bilateral hematomas cases might show rapid and progressive aggravation and should be treated as early as possible, within 19 to 54 hours. Kurokawa et al., showed that 6 of 14 bilateral hematomas cases seemed to show the tendency for a rapid and aggressive clinical course, which often resulted in a poor prognosis or residual neurologic deficits (54), he concluded that bilateral cases should be treated as early as possible with simultaneous decompression of bilateral hematoma pressure, even if the patient shows minimal neurologic deficits.

The mortality rate of anticoagulant-related subdural hematoma can be high up to 13 % and 20% (34, 55). The impact of subdural hematoma is not only on the morbidity and mortality aspects but also on the economic side, as the mean duration of hospital stay of patients with

subdural hematoma usually ranges from 7 to 24 days (31), and the cost totalled \$10,670 (range \$907-238,856) per patient (56).

Because the risk of bleeding is increased while on anticoagulation, the first aim must be to reduce unnecessary use of anticoagulants. A lot of patients could not remember their medication and forget to mention especially antithrombotic therapy, which they often took to reduce symptoms of headache or influenza.

This is important as the age population is expected to rise; therefore the incidence of subdural hematoma is projected to increase over the years. This increasing incidence of the disease call for better health service provision by understanding the pathophysiology of the disease.

### **1.3 Anticoagulation**

However, anticoagulants and antiplatelets are proved to be beneficial in many other conditions such as cardiac conditions, diabetes and many vascular conditions (57, 58), but this comes at the expense of increasing the incidence of chronic subdural hematomas (59). Oral anticoagulant therapy (OAT) is prescribed to large numbers of patients for the prevention and treatment of thromboembolic disease (60). The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin (61).

Many drugs are known to be used with favourable outcomes to the conditions indicated. The oral anticoagulants warfarin, acenocoumarol and phenindione, antagonise the effects of vitamin K, and take at least 48 to 72 hours for the anticoagulant effect to develop fully; warfarin is the drug of choice. If an immediate effect is required, unfractionated or low molecular weight heparin must be given concomitantly. Warfarin act by inhibiting the synthesis of the vitamin K dependent clotting factors (Factors II, VII, IX, and X) and regulatory proteins (proteins C, S, and Z) at the therapeutic dosages they decrease factors

II, VII, IX and X by approximately 30% to 50%, as a result, decreased thrombin is generated and decreased cross-linked fibrin polymer is formed (61). Consequently a defective clotting formation occurs. Subsequently, the cross-linked fibrin polymer is, slowly but continuously, degraded by plasmin to form fibrin degradation products which act by inhibiting the formation of the stabilizing crosslink bonds in soluble fibrin, resulting a greater tendency to rebleed (62). Warfarin has a narrow therapeutic index; thrombosis risk increases when the international normalized ratio (INR) falls below 2.0 and serious bleeding risk increases when the INR rises above 4.0. As a result, major bleeding is a common problem in people taking OAT, occurring at a rate of 2.4%–8.1% per patient-year (63). Heparin is a parental anticoagulants and it initiates anticoagulation rapidly but has short duration of action. It is often referred to as standard or unfractionated heparin to distinguish it from the low molecular weight heparins which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, unfractionated heparin can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion (61). Heparin acts at multiple sites in the normal anticoagulation system inhibiting both extrinsic and intrinsic pathways. Heparin in combination with antithrombin III inactivates the activated factor X and the thrombin. Furthermore, heparin prevents the formation of stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor (61). In addition to its use for deep venous thrombosis, for pulmonary embolism, and in patients after thrombolytic therapy for myocardial infarction, heparin is used during invasive angiographic procedures and cardiopulmonary bypass to prevent thrombus formation.

Antiplatelet drugs decrease platelet aggregation and thrombus formation in the arterial circulation, because in faster-flowing vessels, thrombi are composed mainly of platelets with little fibrin (61). Antiplatelet agents, in particular aspirin and clopidogrel, are an essential component of treatment and prophylaxis for both cardiovascular disease and cerebrovascular; however, they are both associated with a small risk of intracranial hemorrhage (ICH). Clopidogrel effectively inhibits ADP-induced platelet activation and aggregation by selectively and irreversibly blocking the P2Y<sub>12</sub> receptor on the platelet membrane. Interaction of ADP with the P2Y<sub>1</sub> receptor of the platelet induces platelet

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shape change, reversible aggregation, initial glycoprotein IIb/IIIa activation, phospholipase C activation, and calcium flux. Clopidogrel is selective non-competitive inhibitors of the P2Y<sub>12</sub> receptor. Regular use of clopidogrel (75 mg daily) can produce 40%–50% inhibition of ADP-induced platelet aggregation (64). Aspirin acts by irreversibly acetylating the cyclooxygenase (COX-1) enzyme, thus suppressing the production of thromboxane A<sub>2</sub> (TxA<sub>2</sub>) and inhibiting platelet activation and aggregation. This represents the best-characterized mechanism of action, which fully accounts for the unique pharmacodynamics of aspirin as an antiplatelet agent and adequately explains the saturability of its cardio-protective effects (65). The effect of aspirin and clopidogrel on platelets lasts throughout the platelet life span, for about 7 days; therefore, in patient platelet aggregation tests yields abnormal results on admission. Later on, aggregation tests normalized due to transfused platelets and platelets formed de novo in the body (61).

#### **1.4 Why it is important to do this review:**

The aim of this systematic review is to critically appraise and summarise existing information of the effectiveness of anticoagulants/antiplatelets on the clinical outcome of subdural hematoma and to identify areas where further research is needed. The first issue is, whether intracranial bleeds and anticoagulation treatment occur together by chance or if these drugs increase the risk of recurrent and bilateral subdural hematomas. Based on the currently available literature, different studies have different results. A review of the literature has failed to identify a single systematic study and met-analysis of anticoagulation related drugs and recurrent and/or bilateral subdural hematomas, and thus no recommendations can be made regarding the effects of anticoagulation in patients with chronic subdural hematoma. All the current available literatures are from scattered clinical case control studies or cohort studies published previously. Therefore, data about anticoagulants and/or antiplatelets and quality of anticoagulation are often incomplete and divergent and consequently do not allow for any conclusions individually to be drawn. The present review aimed to fulfil this need.

Addressing these issues is crucial as rapid restoration of maximum health potential, especially in the elderly patients, is vital if a chain reaction of medical complications and associated economical consequences are to be averted.

## **1.5 Aims and objectives**

The aim of the study is to perform a systematic review and meta-analysis of studies that examine the effect of anticoagulants/antiplatelets on the clinical course of chronic subdural hematoma and to define groups at high risk for recurrent and bilateral subdural hematoma and thus to contribute to the prevention of these events in patients receiving anticoagulants/antiplatelets treatment. The study also highlights the issue of sensible use of anticoagulants and antiplatelets in medical practice as well. To the best of our knowledge, this is the first systematic review and meta-analysis.

We Used the PICO method to formulate our clinical question:

- Population: all studies about patients with chronic subdural hematoma
- Intervention: all studies about patients with chronic subdural hematoma on anticoagulants/antiplatelets
- Control: all patients with chronic subdural hematoma not on anticoagulants/ antiplatelets
- Outcome: recurrent or bilateral chronic subdural hematoma in patients on perioperative anticoagulation
- The study design is systemic review and meta-analysis of clinical cohort studies
- Primary outcomes:
  - Recurrent chronic subdural hematoma
  - First presentation of bilateral chronic subdural hematoma
- Secondary outcomes
  - To identify those patients on anticoagulation with unknown indications
  - To identify the time period between first and second operation.
  - To identify the time period between trauma and first operation

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- To identify the mortality rate in both recurrent and bilateral groups

## **2. Materials & Methods**

### **2.1 Research protocol**

The PRISMA guidelines (Appendix 1) for reporting of the systematic reviews and meta-analysis were followed to conduct this review. We aimed to identify all studies that examined recurrent and bilateral chronic subdural hematoma related to anticoagulation drugs.

We defined recurrent chronic subdural hematoma as the increase in the volume of the subdural hematoma on the ipsilateral or contralateral to the operated side as seen on CT scan within 6 months of the original drainage procedure and / or occurrence of signs and symptoms attributable to the hematoma seen on CT scan within 6 months of the original drainage procedure. On the other hand, bilateral chronic subdural hematoma as the occurrence of the hematoma on both sides.

Our review protocol consisted of the detailed research question, search strategy, screening criteria for titles and abstracts, and screening criteria for full-text articles. The detailed research question was structured using the patient, intervention, comparison, outcome, study design (PICOS) approach. Our PICOS research question was formulated as follows: does antiplatelet and / or anticoagulant affect the course of subdural hematoma?

Search databases were Medline (using PubMed, Medline at Ovid Online), EMBASE, Scirus, the Cochrane Library, the American Association of Neurological Surgeons (AANS) Database, the conference proceedings of the European Association of Neurosurgical Societies (EANS) and the Google scholar (<http://scholar.google.com>). Search queries were optimised for each specific database. Searches were also carried out on online clinical trial registers; ClinicalTrials (<http://clinicaltrials.gov>) and Current Controlled Trials (<http://controlled-trials.com/mrct>). We handsearched relevant journals and contacted researchers.

After deleting duplicate records, titles and abstracts were screened and included if they represented studies of patients with bilateral and recurrent chronic subdural hematoma on

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perioperative antiplatelet and /or anticoagulant. Studies that specifically reported on other causes of bleeding disorders were excluded.

The PICOS research question was the foundation for study selection, without restriction on publication date, length of follow-up, or publication status. The search also includes studies in other languages with English language abstracts. If anything really useful is identified, it can usually be translated. A manual search of references from the identified papers was then also performed to yield additional papers. We contacted experts in the field and the authors of the identified studies in an effort to identify published, unpublished and ongoing studies.

## **2.2 Search methods for identification of studies**

We used PubMed, Medline and Scirus as our primary data source, and included “subdural hematoma” as a medical subject heading (MeSH) to search with maximum sensitivity. We also searched web-based sources using the search engine Google.com. General internet searches were carried out using selected terms from the original search strategy and individual drug names. Other databases were searched to find additional literature on subdural hematoma such as the Google scholar, Google scholar is also used to find papers that cited the index papers; however, only “subdural hematoma” turned out to be a valid thesaurus term (Medline) or useful keyword (Cochrane Library). Other keywords were queried individually and/or in combination. Details of the search keywords used can be found in Appendix 3. Both English and American spellings were considered. All papers presenting the clinical data regarding the outcome from patients with chronic subdural hematoma on antiplatelet and / or anticoagulant were selected.

## **2.3 Selection of studies**

The author (AE) was responsible for identification and handsearching of appropriate studies for consideration. After screening the database search results, full-text assessment was done for study selection. Two reviewers (AA, MA) independently checked the studies identified by the search strategy to identify potentially suitable studies for the review ac-

cording to the criteria outlined above and eliminate irrelevant studies. Eligible studies will be read fully in duplicate and their suitability for inclusion will be independently checked by both reviewers. We resolved disagreements by discussion with the supervisors (CB, RC) and the outcome of the discussion then managed by consensus. The author assessed the full papers for the type of participants, the type of anticoagulant used, methodological quality, the number of patients excluded or lost to follow up, and the secondary outcome measures stated in the protocol. We excluded publications that clearly did not meet the inclusion criteria at this stage. We retrieved and reviewed the full text of the selected articles and translated in to English where required.

## **2.4 Data Extraction and management**

The author firstly extracted the data into an extraction sheet (Appendix 4). The review authors would have independently checked the extracted data. Any disagreement at any time would have been resolved by discussion among the review authors. After consensus, the author transferred the data to a Microsoft excel datasheet (version 2007 for Windows). Data collection items were extracted into categories. We planned to extract the required information from each included study. As defined in the protocol, data on the following variables were extracted from the selected studies: study design parameters, year of data collection, number of patient on anticoagulants, number of patient not on anticoagulant, number of recurrences in patients on anticoagulant, number of recurrences in patients not on anticoagulant, mortality, unknown indications of the anticoagulation medications, period between the first operation and reoperation, and period between trauma and first operation. The summary of the findings tables will include comparisons between the patients on and not on anticoagulants/antiplatelets. The authors of the selected articles were contacted by emails for any additional data required for the review and information regarding any other studies can be included, they are aware of.

Meta-analysis planned after discussion with the methodology supervisor. We have labelled warfarin, heparin, and related drugs as anticoagulant; aspirin and clopidogrel are categorized as antiplatelet to simplify the analysis.

No external fund is received for the systematic review. To the best of our knowledge, no similar meta-analysis and systematic review has been performed previously. All the studies were carefully scrutinized for inclusion and exclusion criteria.

## **2.5 Types of studies**

All studies comparing respectively the outcome of chronic subdural hematoma caused by anticoagulant and/or antiplatelet.

## **2.6 Types of participants**

### **2.6.1 Inclusion criteria**

- Prospective, retrospective studies and cross-sectional studies.
- All studies that examine the effect of perioperative anticoagulant and / or anti-platelet treatment on the clinical course of chronic subdural hematoma.

We planned to include patients without age, sex, or both spontaneous and trauma patients restrictions. Studies not fulfilling these basic criteria were reviewed to identify other suitable studies but excluded from the analysis.

### **2.6.2 Exclusion criteria**

We excluded from the analysis all the participants of the studies who have history of bleeding disorders or bleeding causes other than anticoagulation therapies. Recurrent subdural hematoma patients in the context of bilateral subdural hematomas were also excluded from the study.

### **2.6.3 Population**

All studies about patients with chronic subdural hematoma

### **2.6.4 Intervention**

All studies about patients with chronic subdural hematoma on anticoagulant/antiplatelet

### **2.6.5 Control**

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All patients with chronic subdural hematoma not on anticoagulant/antiplatelet

## **2.7 Types of outcome measures**

### **2.7.1 Primary outcomes**

- Recurrent chronic subdural hematoma
- First time presentation of bilateral chronic subdural hematoma.

### **2.7.2 Secondary outcomes**

- To identify those patients on anticoagulation with unknown indications
- To identify the time period between the first and second operation.
- To identify the time period between trauma and first operation
- To identify the mortality rate in both the recurrent and bilateral categories

## **2.8 Potential confounders**

Bilateral subdural hematoma is itself a risk factor for developing recurrent subdural hematoma. Any study reporting recurrence in the context of bilateral subdural hematoma is excluded from the recurrent group.

## **2.9 Data collection**

See appendix 5 for data collection sheet.

## **2.10 Data collection procedure**

- The author/investigator was the main data collector from the studies
- Missing data were handled by contacting the authors of the index papers and more search for other studies to be included using the criteria outlined above

## **2.11 Data protection**

- All relevant information in this study were handled in line with data protection rules

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- No ethical approval was needed for this study. The study protocol was in accordance to the guidelines of the ethics committee at our university, Royal college of Surgeons in Ireland.
- Informed consent is not required in our study as all our data were collected from published articles. However we did ensure patient's anonymity was maintained during our contact with authors for missing data.

## **2.12 Assessment of risk of bias**

We investigated also any sources of bias. We intended that at least two authors will assess the internal validity of individual trials, using the Cochrane Collaboration's risk of bias tool as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Using the data extraction sheet developed for this review, the author extracted relevant data and this was compared and discussed with the reviewers until consensus was achieved and a recommendation made for inclusion or exclusion from the review. We entered details in a risk of bias table designed by the author and adopted from the Cochrane handbook (Appendix 5), for each included study, indicating the methodology, mainly concentrating on the stratification of the author of the article for the other different causes of bleeding disorders, other selection bias, performance bias, attrition bias, detection bias and confounding factors, and reporting bias. Two reviewers (MA and AA) independently evaluated the risk of bias of the included studies. The risk of bias in each domain was rated as high risk, low risk, and unclear. Any disagreement again between the reviewers was resolved by consensus.

## **2.13 Assessment of heterogeneity**

Before pooling any data for analysis, we considered whether or not there was substantial clinical heterogeneity between the studies. We planned to examine the participants, interventions, and outcomes of the studies for evidence of clinical heterogeneity. We explored heterogeneity and performed subgroup analyses as appropriate. We considered subgroup analysis by different types of drugs. However following consideration of the

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data available from the included studies we only performed subgroup analysis into the types of anticoagulation for recurrent hematomas. If heterogeneity encountered, we would have inspected the outlier studies to determine the cause. If clear reasons for the heterogeneity were found, we would not have added the responsible studies to the main body of homogeneous studies, but would have summated and presented them separately and indicated the reasons for heterogeneity. Additionally, we would have used the I-squared statistic to quantify the extent of heterogeneity. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. If the I-squared estimate was greater than 50%, we would have interpreted this as indicating the presence of considerable levels of heterogeneity. We planned that if there was any evidence of clinical or statistical heterogeneity; we would not conduct a meta-analysis and would report findings in a narrative form. Then, we considered the appropriateness of pooling and meta-analysis was performed.

## **2.14 Statistical analysis**

All statistical analysis was performed using the StataIC 12 software for Windows (StataCorp College station, Texas, USA). Throughout the analysis, a p-value of less than 0.05 was considered significant. To identify risk factors for the development of recurrent and bilateral chronic subdural hematoma, we calculated relative risk ratios (RR) and corresponding 95% confidence intervals (CI).

## **3. Results**

All studies included in this review were clinical cohort studies comparing respectively the outcome of chronic subdural hematoma caused by anticoagulant and/or antiplatelet.

### **3.1 Study Identification**

A PRISMA 2009 flow diagram is followed for the search strategy (Figure 1, Appendix 2). The search strategy yielded 157 of articles, of which 104 were excluded based on title or abstracts. Fifty one full text articles were assessed for eligibility. Only 11 articles of the

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remaining fifty one articles met our inclusion criteria and were included in the systematic review.

### **3.2 Study characteristics**

The search strategy yielded a total of eleven studies that fit the above criteria. Three studies are based in Japan (27, 28, 47), two in Germany (48, 66), one in the united kingdom (49), one in Australia (32), one in Ireland (46), one in Korea (67), one in France (68), and one in Taiwan (69). Nine studies for the recurrent subdural hematoma (Table 1) and two studies for the bilateral groups (Table 2). There is a broad international variation in the countries where the studies took place.

The size of participants in the included bilateral studies ranges from 129 (67) to 236 (68) participants, and for the recurrence ones from 81(32) to 500 (27) participants. In total, 1854 and are included in the meta-analysis for the recurrent. No meta-analysis was attempted for bilateral subdural hematomas. 365 patients were studied for the bilateral category. All the eleven studies used the same study design to identify the patients. One study was in French language with English abstract. Translation was done with the help of Google translator and contacting the experts in French language. Of these eleven requests sent to the author of the studies, none were answered at the time of writing the thesis. The summary of the findings include comparisons between the recurrent hematoma patients on and not on anticoagulant/antiplatelet groups (Table 3, Table 4).

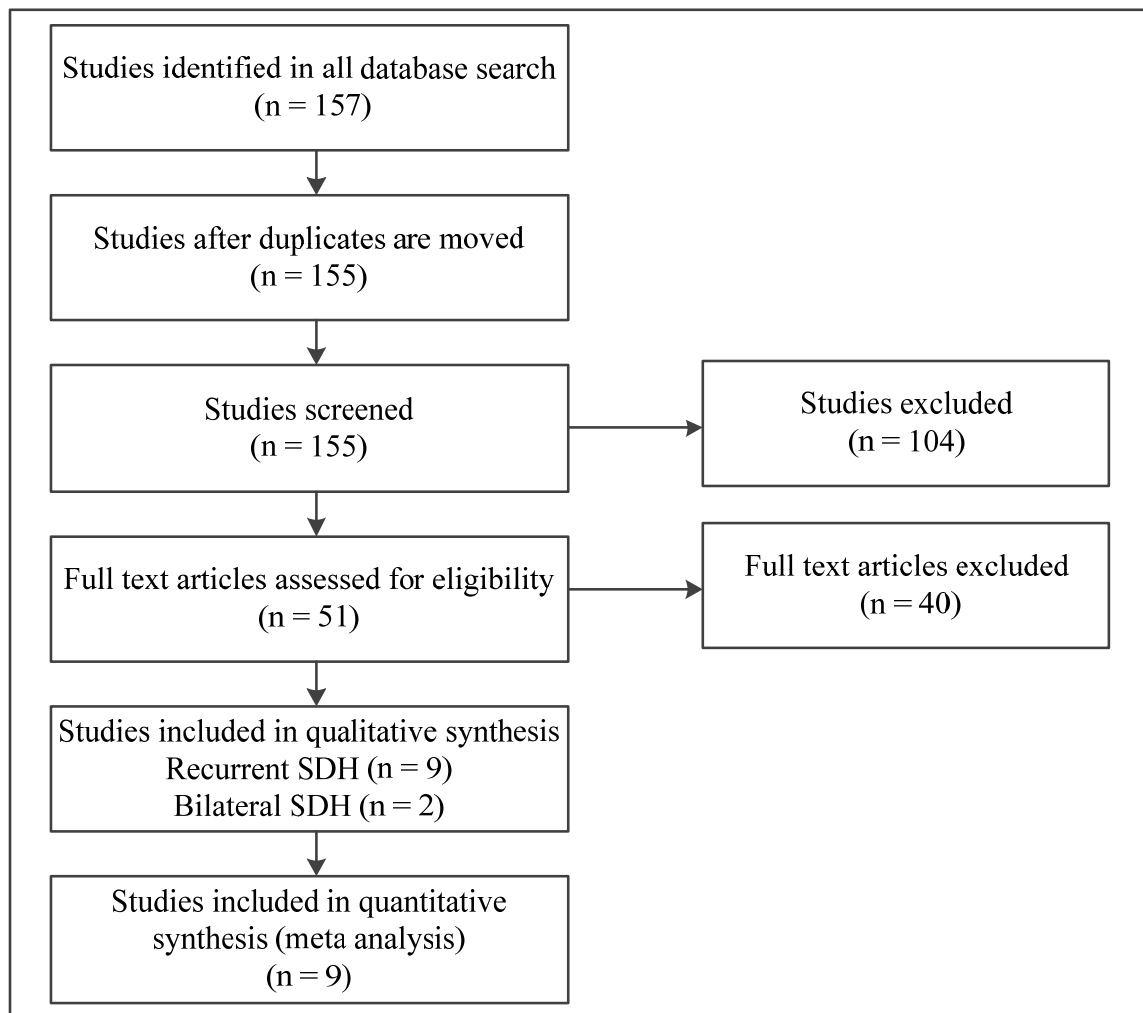


Figure 1. PRISMA flow diagram of search strategy.

Table 1. Included studies of the recurrent subdural hematoma

The study	Study year	Type of the study	Number of patient studied
O'Brien et al. (46)	1994-1997	Clinical Cohort Study	123
Buxton et al. (49)	1990-1992	Clinical Cohort Study	34
Buxton et al. (49)	1995-1997	Clinical Cohort Study	150
Konig et al. (48)	Two years period	Clinical Cohort Study	114
Forster et al. (66)	Consecutively admitted patients	Clinical Cohort Study	144
Byung et al. (67)	2001-2006	Clinical Cohort Study	255
Torihashi et al. (47)	2003-2007	Clinical Cohort Study	337
Rust et al. (32)	1996-2001	Clinical Cohort Study	81
Oishi et al. (28)	1995-1999	Clinical Cohort Study	116
Mori et al. (27)	1987-1999	Clinical Cohort Study	500

Table 2. Included studies of bilateral subdural hematoma

The study	Study year	Type of the study	Number of patients studied
Tsai et al. (69)	2002-2005	Clinical Cohort Study	129
Penchet et al. (68)	1990-1995	Clinical Cohort Study	236

Table 3. Summary of the data of recurrence on anticoagulant

The study	Number of patients studied	Anticoagulant	Patient not on anticoagulant	Patient on anticoagulant	Recurrence off anticoagulant	Recurrence on anticoagulant
O'Brien et al.	123	Anticoagulant	30	15	2	3
Buxton et al.	184	Anticoagulant	150	34	22	5
Forster et al.	144	Anticoagulant	40	66	0	22
Byung et al.	255	Anticoagulant	247	8	18	1
Konig et al.	114	Anticoagulant	84	21	16	2
Rust et al.	81	Anticoagulant	46	17	8	2
Torihashi et al.	337	Anticoagulant	275	11	47	2
Torihashi et al.	337	Both*	275	13	47	2
Oishi et al.	116	Both*	105	11	6	0
Mori et al.	500	Both*	474	26	23	9

\* anticoagulant & antiplatelet

Table 4. Summary of the data of recurrence on antiplatelet

The study	Number of patients studied	Anticoagulant	Patient off antiplatelet	Patient on antiplatelet	Recurrences off antiplatelet	Recurrences on antiplatelet
O'Brien et al.	123	Antiplatelet	30	78	2	10
Forster et al.	144	Antiplatelet	40	38	0	12
Konig et al.	114	Antiplatelet	84	9	16	2
Rust et al.	81	Antiplatelet	46	18	8	7
Torihashi et al.	337	Antiplatelet	275	38	47	10



Table 5. Summary of the data of bilateral chronic subdural hematoma

The Study	Number of patients studied	Anticoagulation	Patient off anticoagulation	Patient on anticoagulation	Bilateral not on anticoagulation	Bilateral on anticoagulation
Tai et al	129	Both*	118	11	44	11
Penchet et al	236	Both*	179	57	40	9

\* anticoagulant & antiplatelet

### **3.3 Risk of Bias**

Low risk of bias was identified in the included studies for the recurrent subdural hematoma. We did not do any analysis for the bilateral subdural hematoma because all the studies of the bilateral category encountered did not specify the types of the anticoagulation drugs used. In the recurrent subdural category, three studies failed to report the type of anticoagulant/antiplatelet drug used, and they are excluded from the analysis of the homogenous groups. The analysis of these three studies was presented separately (Figure 1).

### **3.4 Effects of intervention**

#### **3.4.1 Recurrent Subdural Hematoma**

The analysis of antiplatelets shows a significant increase in risk, with a pooled relative risk of 1.88, and no significant heterogeneity between studies (I-squared = 26.5%,  $p = 0.245$ ). For anticoagulants, however, the pooled relative risk was only 1.26 and it was not statistically significant. Again, there is no significant heterogeneity (I-squared = 40.8%,  $p = 0.119$ ). Finally, the studies that failed to distinguish between the antiplatelets and anticoagulants show a mixed picture, with significant heterogeneity (I-squared = 83.0%,  $p = 0.003$ ). This is important because it can explain that the effect would depend on the precise admixture of the two treatment regimes. The Overall outcome of the recurrent subdural hematoma I-squared is 58.6%, and p-value equal to 0.002. The heterogeneity is encountered when we combined the both data of the anticoagulant and antiplatelet drugs together into one category, but this is solved by stratification the data of the medications into two subgroups after careful reviewing the design of the studies included in the review (Figure 2).

#### **3.4.2 Bilateral subdural hematoma**

Regarding the bilateral subdural hematoma, the included studies did not differentiate between the anticoagulant and antiplatelet drugs. The analysis shows a significant increase in risk, with

a pooled relative risk of 1.34 ( $p = 0.000$ ) (Figure 3). The overall I-squared was 96.8% and this indicates significant heterogeneity. Given the lack of high-quality studies and the heterogeneity of the data from the available studies pointing to the possibility of bias, we did not perform meta-analysis for the bilateral category. Out of the 129 patients studied retrospectively by Tai eleven were received anticoagulation medications. Bilateral was noted in all of them. However, in the retrospective analysis of Penchet nine patients developed bilateral subdural hematomas of the 57 participants who are on anticoagulant (Table 5).

### 3.4.3 Unknown indication of anticoagulation

The unknown indication of treatment category was defined as when the indication of the anticoagulation treatment was unknown to the patient, the relatives, nor the neurosurgical team. Both O'Brien and Buxton reported at different time periods that patients who had no indication for anticoagulation was approximately 20%. This means that one in every five patient the indication of the anticoagulation drugs were unknown (Table 6).

Table 6. Unknown indication of anticoagulation

The study	Unknown indication of anticoagulant
O'Brien et al.	24 (20%)
Buxton et al.	7 (21%)

### 3.4.4 Time period to operation and reoperation

Buxton found that all recurrences of subdural haematoma occurred within 3 weeks of the first operation. According to Torihashi et al., the time interval between the injury and the first operation for patients with antiplatelet and/or anticoagulant therapy ( $29.9 \pm 26.5$  days) was shorter than that for patients without it ( $44.2 \pm 26.6$ ) ( $P = 0.022$ ). In contrast, the average time between the first operation and the second operation was  $33.4 \pm 18.2$  days for patients who had received antiplatelet and/or anticoagulant drugs, compared with  $34.2 \pm 24.9$  days for patients who had not ( $P = 0.897$ ). Mori in 2001 found that recurrence of hematoma was

recognized at 1-8 weeks after the first operation. Furthermore, the interval from trauma to first operation was 7.2 +/-3.8 weeks in patients with recurrence and 8.5 +/-5.0 weeks in patients without recurrence but this difference was not statistically significant to him (Table 7).

Table 7. Time period to operation/reoperation of participants

The study	Time to reoperation	Time to operation
Buxton et al.	within 3 weeks	N/A
Torihashi et al.	33.4 +/-18.2 days	29.9 +/- 26.5 days
Mori et al.	1-8 weeks ( Mean: 3.5+/-1.9 weeks)	7.2 +/- 3.8 weeks

### 3.4.5 Mortality

Mori have six patient (1.2%) died in his analysis, Forster five patients (3.5%), Buxton three patients (0.02%), Konig four patients (3.5%), and no death for Torihashi in the recurrent group (Table 8). However, the bilateral categories, both Tsai and Penchet reported a mortality rate of 2 (4%) and 5 (2.6%) patients, respectively (Table 9).

Table 8. Mortality rate of recurrent chronic subdural hematoma

The study	Mortality rate
Buxton et al.	3 (0.02%)
Konig et al.	4 (3.5%)
Forster et al.	5 (3.5%)
Torihashi et al.	0
Mori et al.	6 (1.2%)

Table 9. Mortality rate of bilateral chronic subdural hematoma

The study	Mortality
Tsai et al.	2 (4%)
Penchet et al.	5 (2.6%)

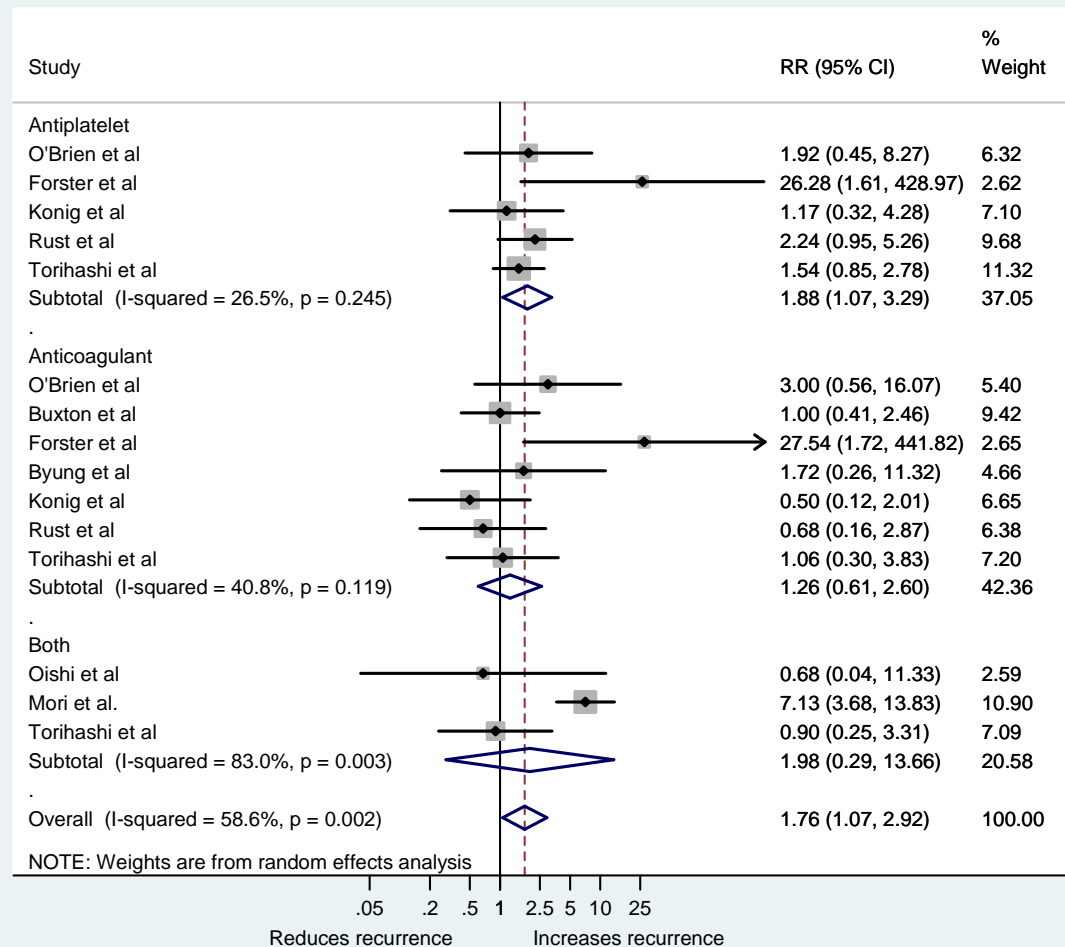


Figure 2. Meta-analysis of the antiplatelets/anticoagulant related recurrent chronic subdural hematoma

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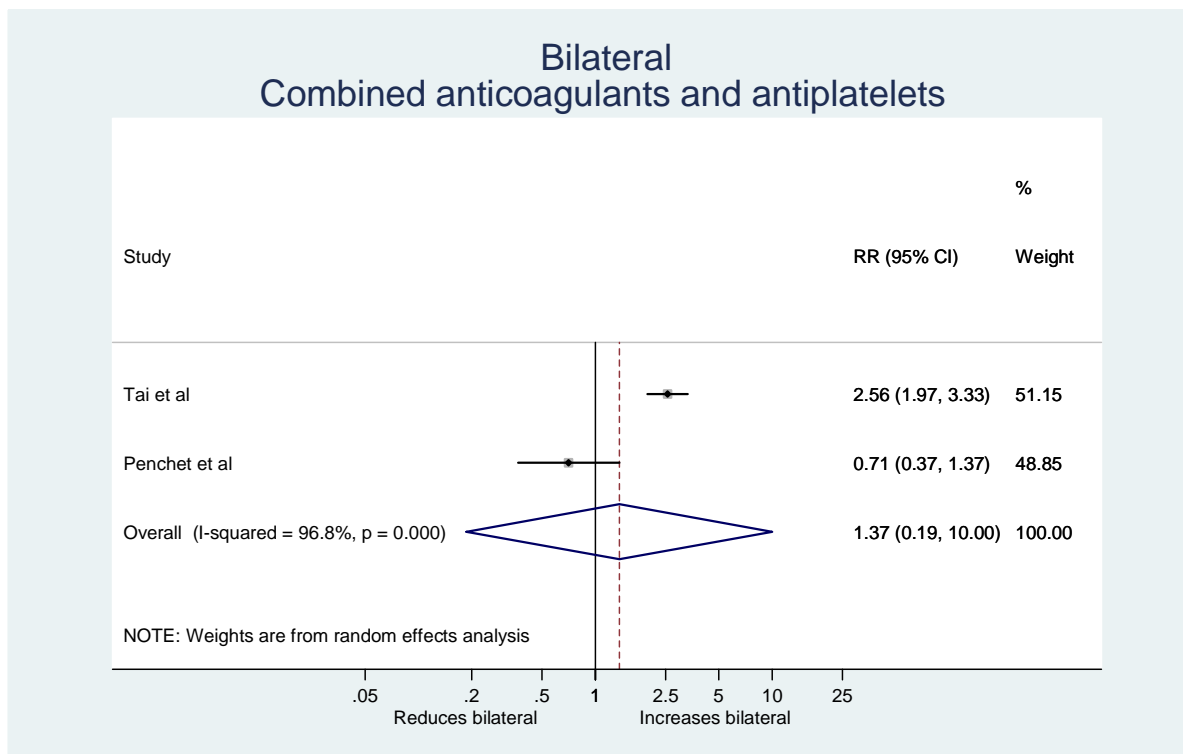


Figure 3. Meta-analysis of the anticoagulants related bilateral chronic subdural hematoma

## **4. Discussion**

### **4.1 Statement of principle findings**

The aim of this review was to evaluate the effects of anticoagulation therapy on the clinical course of chronic subdural hematoma, in terms of development recurrent or bilateral subdural hematoma. Given the conflicting results regarding the use of anticoagulation related drugs in patients with bilateral or recurrent CSH, it is disappointing that there are no randomised controlled trials (RCTs) that evaluated their effectiveness in those patients with chronic subdural hematoma. We identified only retrospective or clinical cohort studies.

The analysis of antiplatelets shows a significant increase in risk, with a pooled relative risk of 1.88, and no significant heterogeneity between studies (I-squared = 26.5%,  $p = 0.245$ ). For anticoagulants, however, the pooled relative risk is only 1.26 and it was not statistically significant. Again, there was no significant heterogeneity (I-squared = 40.8%,  $p = 0.119$ ). Finally, the studies that failed to distinguish between the antiplatelets and anticoagulants showed a mixed picture, with significant heterogeneity (I-squared = 83.0%,  $p = 0.003$ ). This is important because it can explain the effect would depend on the precise admixture of the two treatment regimes.

### **4.2 Context of previous studies**

Although our systematic review is the first review assessing the impact of the anticoagulant and or antiplatelet on the clinical course of chronic subdural hematoma. Regarding the anticoagulant, our findings are consistent with other studies that showed there was no statistical significance in the recurrent group (47-49). Regarding the antiplatelet, our result identified a significant result with recurrent. There is some uncertainty as to the impact that aspirin has on the

risk of sustaining intracranial hemorrhage. In two case control studies, aspirin in its usual prophylactic dose did not significantly increase the risk of intracerebral bleeding (70, 71). Another study found no statistically significant difference in recurrence of hematoma in patients who did (32%) and did not (13%) receive antiplatelet agents preoperatively (66). One review claimed that aspirin would double the risk of intracerebral bleeding, regardless of dose (72). This conclusion was reached on the pooled data from four randomized controlled trials of combined oral anticoagulant and aspirin use in patients with prosthetic heart valves, and may therefore be subject to selection bias. Torihashi et al. restarted antiplatelet medications one week after surgical intervention. These authors observed no significant difference in the frequency of chronic subdural hematoma recurrence between those patients with a history of antiplatelet medications and those without such a history (47). In contrast, a single-center study of 81 patients presenting with chronic subdural hematoma who underwent evacuation of their lesion found that a significantly higher proportion of patients with a history of aspirin (39%) underwent reoperation for recurrent chronic subdural hematoma than did those patients either on warfarin (21%) or without any history of anticoagulation/antiplatelet medication (28%) (32). It is generally assumed that the prognosis of oral anticoagulant-related intracranial hemorrhage is worse than bleeds unrelated to oral anticoagulant use, mainly because of the greater chance of extension (73). Six studies found the bleeding risk to be strongly related to the intensity of oral anticoagulation, with a RR 1.4–1.8 for every unit increase starting from international normalized ratio (INR) 2.0, and a RR 3.0–7.9 for  $\text{INR} \geq 4.5$  (74-78). Most reports dealing with anticoagulant related intracranial hemorrhage have discussed the duration of therapy on the risk of bleeding. One opinion is that the risk of an intracranial hemorrhage is increased in the first months after starting oral anticoagulant therapy (79-82), while an alternative view states that the risk of sustaining an intracranial bleed increases with increasing length of therapy (34, 83).



The proportion of patients found to be overanticoagulated has generally ranged from 6% to 38% of patients (34, 79, 83-87), while the intensity has also been reported to be 'subtherapeutic' in up to 28% of patients (34, 80, 87). However, the international normalized ratio values determined upon admission do not necessarily reflect the international normalized ratio at the time of sustaining a haemorrhage. Caution is thus warranted when making inferences on the risks associated with intensity of oral anticoagulant therapy from INR values measured on admission (85).

Mattle et al. (34) suggest that as many as one-third of patients, having intracranial haemorrhage, whilst on warfarin, may not actually need to be on it. Furthermore, a study by Buxton et al.(49) showed that seven patients had no indication for warfarin in their notes.

Mortality varies in the literature between the series from 2% to 4.3% (21, 40, 59, 88). A high mortality index in the postoperative period was found in patients with INR (international normalized ratio) values greater than 1.25 and/or thrombocytopenia ( $p < 0.001$  and  $p = 0.004$  respectively), a mortality of 9.3% of patients treated for this condition (89). One study reported that both overall mortality (OR = 4.48, 95% CI 1.60-12.50,  $p = 0.004$ ), and mortality after Intracranial haemorrhage (OR = 3.42, 95% CI 1.09-10.76,  $p = 0.03$ ) was increased in the therapeutic as compared with the nonuser group (90). According to the current analysis, the mortality in the bilateral group is more than the recurrent subdural hematoma. This is reported in previous studies and explains the aggressive course of the disease and the importance of the early identification.

### **4.3 Strengths and weaknesses**

There is a risk of publication bias in all systematic reviews. In an effort to minimise this we searched extensively for relevant literature in databases, handsearched conference abstracts and contacted trial authors and experts in the field for unpublished and ongoing trials. We are

confident that our detailed search strategy combined with handsearching identified all relevant trials. However, it is still possible that we did not identify some 'grey' literature. It would be unlikely, however, that this would have a significant impact on our results. No statistical or graphical evidence for publication bias was detected in the selected articles.

We have reported the findings of nine studies of recurrent subdural hematoma and two studies of bilateral subdural, all of them related to anticoagulation caused by medications and we believe they were the only published studies that satisfied our inclusion criteria at the time of our search. The weakness of this review was the small number of studies included in the analyses and the heterogeneity mainly encountered among the bilateral groups due to the lack of reporting of the type of anticoagulation drug in the original study. We noted the exclusion of several potentially relevant trials solely on the basis that they had not included any clinically relevant outcome measures and absence of control. This limitation considerably reduced the power of this review to reach reliable conclusions and we urge future researchers to include such outcomes in their clinical trials. The strengths of our study are that it addresses a question that is potentially of enormous clinical and public health importance using different clinical cohort studies. This study pools data from a range of studies from different locations and time periods, and therefore enhances the generalisation of its findings. The results of this study should be interpreted in the context of the review limitation and scarcity of the available relevant studies. Therefore, we recommend that further multicentre studies/trials with larger sample sizes be undertaken to evaluate the efficacy of different anticoagulation therapies on chronic subdural hematoma. Moreover, the quality of the included studies was measured by using a validated method for assessing the quality. In addition, two reviewers independently assessed both the quality of the included studies, risk of bias and the data extracted.

## 4.4 Clinical implications

The two most common conditions requiring chronic anticoagulation are prosthetic heart valves and chronic atrial fibrillation. Atrial fibrillation is the most common arrhythmia encountered in clinical practice, in prospective studies, the incidence is <0.1% per year in patients <40 years old and reaches 1.5–2% per year in those >80 years old (91). Mechanical heart valves are thrombogenic and require long-term anticoagulant therapy. The incidence of prosthetic valve thrombosis in patients not anticoagulated or taking anti-platelet drugs is 1.8% per patient / year. The incidence of embolism resulting in death, stroke, or peripheral ischemia requiring surgery is 4% per patient / year and this is reduced to 1.0% per patient year with anticoagulant therapy (92).

The most common anticoagulant medication in the literature implicated in the development of chronic subdural hematoma is orally administered warfarin (93). Adjusted dose warfarin has been shown to reduce stroke incidence by 62% in patients with chronic atrial fibrillation (39). This benefit was not offset by the occurrence of major hemorrhage. The rate of intracranial hemorrhage is approximately 0.3% per year for patients receiving warfarin with a maintained international normalized ratio of 2.0 to 3.0. The rate of stroke among patients with chronic atrial fibrillation who are not receiving anticoagulation ranges from 5% to 12% per year (55, 94). A recent meta-analysis showed that adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation (95). Evidence supports the safety of temporary interruption of anticoagulation therapy for 1 to 2 weeks in patients with intracranial hemorrhage and mechanical valves or atrial fibrillation (96, 97).

Current guidelines for reversal of oral anticoagulant related anticoagulation are the use of vitamin K, FFP, or factor concentrates (34, 98-101). The simplest method of reversal is the withholding of 1 or more doses of the vitamin K antagonist. Although the coagulopathy begins to correct within 24 to 36 hours, it will not fully correct for 3 to 5 days; therefore, this method is only appropriate for an asymptomatic patient with an elevated INR or a very minor bleed (102). The correction may take 9 hours with standard FFP and with factor IX complex in conjunction with FFP it may take 2.93 hours (99). In addition to the time factor, FFP infusion can cause fluid overload as a result of the number units required to reverse anticoagulant and the impaired renal and cardiac functions in this age groups (103). Alternative to FFP for the reversal of warfarin include prothrombin complex concentrate (PCC), which includes the vitamin-K dependent coagulation factors II, VII, IX and X. This permits complete reversal with a bolus infusion over a period of three minutes without hemorrhagic or thrombotic adverse effect observed intra- or post- operatively (104). Whereas PCC can be rapidly prepared and corrects vitamin K antagonist-induced impairment of hemostasis within 30 minutes of administration, FFP must be thawed and large volumes infused, leading to delayed and often inadequate correction of anticoagulation (102, 103). Prothrombin complex also offers safety advantages over FFP, such as virus reduction/inactivation and a low risk of thrombotic events (104-106). FFP is associated with transfusion-related lung injury, allergy/anaphylaxis, hemolysis, and bacterial contamination/sepsis (107). Another complex used for the reversal of oral anticoagulant include recombinant - activated factor VII (rFVIIa), it was used to rapidly reverse excessive warfarin induced anticoagulation (108). It appears that rFVIIa may be the best candidate to date for reversal of coagulopathy in intracranial hemorrhage (109). This agent was found to be helpful in reversal of intraoperative coagulopathy that proves refractory to the traditional methods. However, the role of rFVIIa remains unclear given the known side effects of thromboembolic adverse events with its extremely high cost (110-112). The sug-

gested optimal coagulation parameter at which neurosurgical procedures can be performed is an INR of at least 1.4 or less (86, 99). Given the potential for adverse thrombotic events associated with reversal of coagulopathy (104, 113), a more gradual reversal technique, such as the administration of vitamin K, can be decided in non critical conditions, when initial conservative management is planned (114). This is accomplished by administering up to 10 mg of vitamin K via slow intravenous infusion, followed by oral supplementation of 1 or 2 mg (93). According to Boulis et al., he found an accelerated correction of coagulation in the factor IX complex concentrate group and a higher complication rate for the FFP-treated group when compared the use of fresh frozen plasma (FFP) and factor IX complex concentrate in anticoagulation treated patients with intracranial haemorrhage. Another advantage of factor IX complex concentrate is the less volume load compared with FFP (99). Heparin and heparin derivatives, on the other hand, can be counteracted by protamine sulphate (115). Protamine sulfate irreversibly binds to heparin, thereby neutralizing its anticoagulant effect, and is the only drug clinically available for this purpose. Used according to established guidelines, protamine is a relatively safe and effective drug, but serious adverse reactions may occur. The exact incidence of severe reactions, including respiratory compromise, hypotension, and shock, varies from 0.2% to 3% in a general population (116).

Reintroduction of anticoagulation should be based on the balance between a patient's thromboembolic risk and their bleeding risk. When the risk is equal for both, use of intravenous unfractionated heparin may be considered (98). Anticoagulation with enoxaparin after mechanical heart valve replacement has been found to provide adequate biological anticoagulation, and compares favourably with unfractionated heparin anticoagulation (117). Enoxaparin, a low molecular weight heparin, has been found to be effective and relatively safe substitute anticoagulant for patients with mechanical heart valves who must withhold oral anticoagulant (118). In the patient with subacute SDH no hematoma expansion was noted during the period

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of treatment with unfractionated heparin and nadroparin calcium. In 2010, Forster et al. (66), reported the significant increase in the risk of reoperation with the duration and dose of post-operative application of low molecular weight heparin (nadroparin; molecular weight 4500 daltons). Of 66 patients were postoperatively treated using LMWH, 22 (33%) had to undergo reoperation while the remainder did not, with a median duration of the treatment of 18 days and 10 days, respectively ( $p < 0.01$ ). The daily median dosage of treatment was 5700 IU in the patients who required reoperation and 2850 IU for those who did not ( $p < 0.05$ ). Discontinuation of oral anticoagulant therapy for about 2 to 3 weeks has comparatively a low probability of embolic events in patients with mechanical heart valve (109, 119). Strikingly, Wijdicks et al. (97) feels that the risks of stopping warfarin for neurosurgical intervention are small even for up to 2 weeks. Buxton et al., confirmed stopping warfarin over a shorter period of 3–5 days without detectable harmful effect (49). One study have showed that failure to achieve reversal of anticoagulation preoperatively may be associated with poor outcome (120). Even in patients with compelling indications for anticoagulation such as patients with prosthetic heart valves reversing anticoagulation is still necessary, as arresting intracranial bleeding is paramount.

Patients with chronic subdural hematoma who undergo reversal of anticoagulation prior to surgical treatment do not experience additional post-operative morbidity and increased rates of recurrence relative to patients without a requirement for anticoagulation (121). Both Buxton and Kawamata et al., also found that early resumption of anticoagulant therapy (within 3 days) did not result in intracranial rebleeding in any postoperative patient. Both authors recommend resuming anticoagulants after an interval of 3 days in those patients with mechanical heart valves (49, 120). In those patients whose anticoagulant medications were restarted post-operatively, recurrence rates ranged from 6% to 10% (49, 120), while in those who were not restarted, the rate was 22% (49). Additionally, the rates of thrombotic complications for

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patients off anticoagulation (0–10%) did not vary significantly from patients without baseline anticoagulation requirements (49, 120). In his experience, König et al. (48) described that patients under anticoagulative medication, being treated with coagulation factors preoperatively, reach an outcome level comparable with those patients without any coagulation disorders. Therefore, it seems to be a benefit to perform subtle correction of anticoagulation before surgery.

Aspirin is the most widely used treatment to prevent cardiovascular disease because it is inexpensive and highly effective, reducing the risk of myocardial infarction, stroke or cardiovascular death by about 20% in a broad range of patients at high-risk of future cardiovascular events (122). Most commonly, patients on antiplatelets planned for subsequent evacuation of the chronic subdural hematoma undergo reversal of the antiplatelet agents prior to intervention. This can be accomplished through platelet transfusion (123) and/or desmopressin administration (124); however, no studies to date have rigorously analyzed the efficacy of such therapy in the setting of chronic subdural hematoma. Recently a study conducted by Li found that platelets aggregation recovers within 4 days of stopping aspirin but clopidogrel must be stopped for 10 days to achieve a normal aggregatory response (125). Use of aspirin in primary prevention of cardiovascular events, in patients with or without diabetes, is of unproven benefit. Long-term use of low-dose aspirin is of benefit in established cardiovascular disease (secondary prevention). On the other hand, it seemed also to increase the incidence of hemorrhagic stroke both in the primary and in the secondary prevention trials (126).

The most efficient way to reduce its occurrence of recurrent or bilateral is to check the indication for anticoagulant treatment over and over again. On the other hand, the fear of bleeding complications should not restrain the physician from antithrombotic therapy, and after haemorrhage it should not restrain the physician from restarting the anticoagulant medication fol-

lowing an appropriate time period either. Some of the patients do not die because of the intracranial bleed. They die after discontinuation of anticoagulation because of the disease for which the treatment was being given.



## **5. Conclusions**

### **5.1 Implications for practice**

Anticoagulants do not appear to have an effect on the clinical course of chronic subdural hematoma, although more studies need to be done to confirm it. Anticoagulants are effective in reducing stroke related to atrial fibrillation and prosthetic heart valves as well as they are reasonably reversible. Antiplatelets drugs were found to be significantly affect the outcome of subdural hematoma. On the balance, our study recommends the use of anticoagulants compared to antiplatelets when indicated. The study also recommends the utmost important of both the accuracy of diagnosis and the strength of indication before starting oral anticoagulant therapy. The need for regular monitoring of the drug is of course self-evident, and the lowest effective target INR for each individual indication should be recommended. In conclusion this study emphasis the use and lowest effective anticoagulation for each individual indication should be recommended. Clinicians must balance the potential benefit against the risk of complications in each case.

### **5.2 Implications for research**

There is the need for more well designed prospective and randomized controlled studies to explore the issue more thoroughly. It also would be helpful if future studies on anticogualtion medications reported the types of drugs involved in the study. More studies are needed to investigate the role of classical and new anticoagulants and antiplatelets on chronic subdural hematoma. Therefore, our study aims to determine the effect of perioperative anticoagulation drugs on the clinical course and postoperative outcome of chronic subdural hematoma patients. There is a need for more clinical studies with adequate sample sizes to detect clinically important differences and using established outcomes to add weight to the results we have obtained.

The contents of the enclosed manuscript are confidential and should not be disclosed, or disseminated in any way, to any third party other than to staff or students of the Royal College of Surgeons in Ireland or an external examiner appointed for the purpose of reviewing the manuscript.

**Competing interest**

The author declare that they have no competing interest

**Author Contribution**

The author (AE) involved in the study conception, design, and data collection and performed the systematic search of the literature. Both AA and MA independently evaluated potential articles, the methodological quality of studies and source of bias and the extracted data. The statistical analysis performed and interpreted was done with the help of RC. CB read and approved the final manuscript.

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# Appendix 1. PRISMA 2009 checklist



## PRISMA 2009 Checklist

Section/topic	#	Checklist Item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	

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## PRISMA 2009 Checklist

Section/topic	#	Checklist Item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

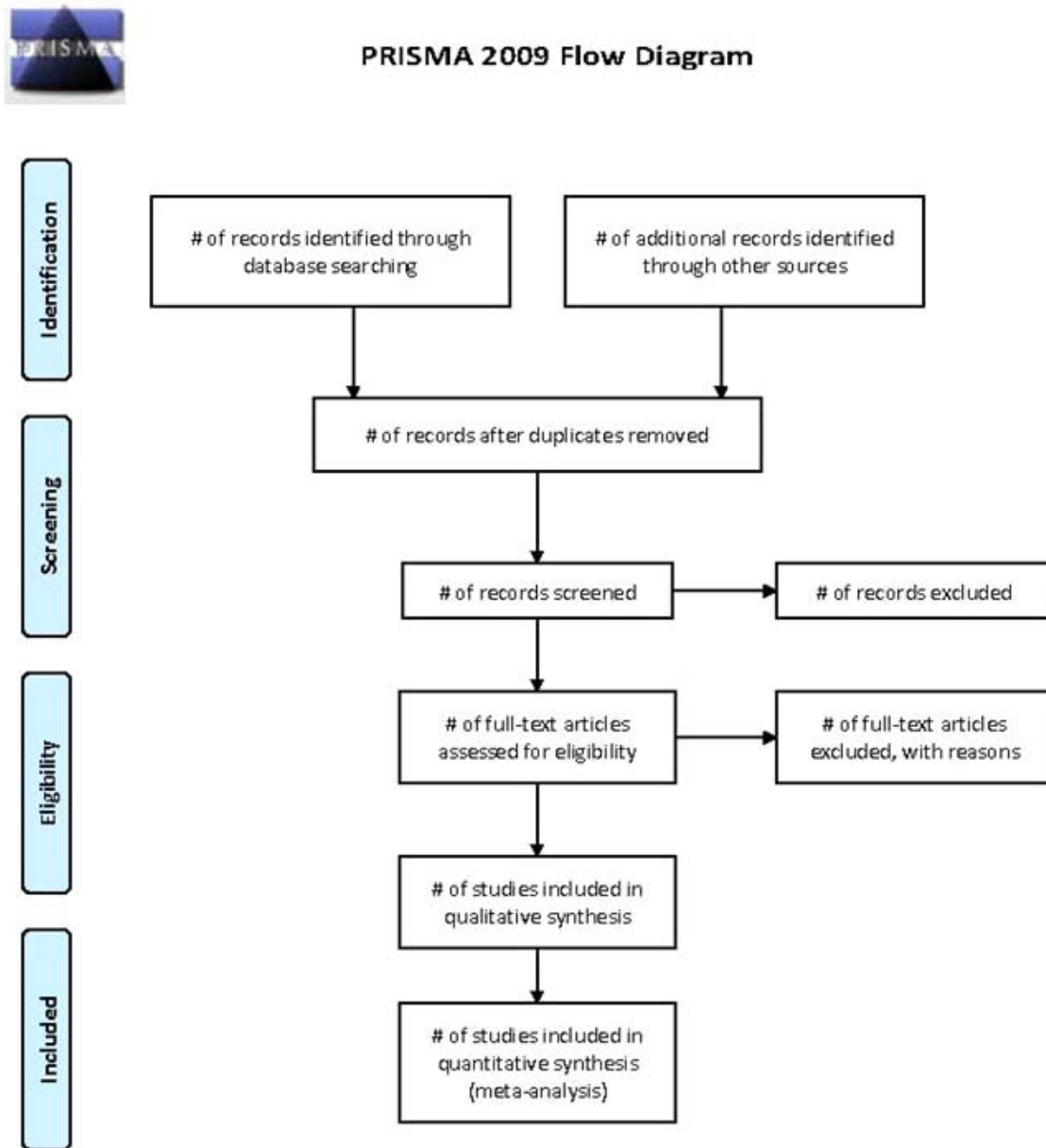
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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## Appendix 2. PRISMA 2009 flow diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit [www.prisma-statement.org](http://www.prisma-statement.org).

### Appendix 3. Search keywords

1. subdural, chronic/
2. subepidural\*
3. hematoma.tw
4. haematoma.tw
5. hematom\*.tw
6. haematom\*.tw
7. hemorrhag\*.tw
8. haemorrhag\*.tw
9. subdur\* or extracran\*.tw
10. chron\*.tw
11. bleed.tw
12. anticoagulants.tw
13. anticoagulan\*.tw
14. anticoagula\*
15. aspirin.tw
16. warfarin.tw
17. clopidrogel.tw
18. heparin.tw
19. antiplatelet\*
20. pachymening\*
21. extracran\*
22. Anticoaguls\* or antiplate\*
23. randomized controlled Trial, controlled clinical trial.tw
24. clinical trial.tw
25. vitamin K antagonist.tw
26. coumadins.tw
27. antithrombin.tw
28. low molecular weight heparin
29. LMWH.tw
30. enoxaparin.tw
31. dalteparin.tw
32. tinzaparin.tw
33. bemiparin.tw
34. certoparin.tw
35. nadroparin.tw

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36. parnaparin.tw
37. reviparin.tw
38. cyclooxygenase inhibitors.tw
39. adenosine diphosphate receptor inhibitors.tw
40. ADP receptor inhibitors.tw
41. plavix.tw
42. prasugrel.tw
43. effient.tw
44. ticagrelor.tw
45. brilinta.tw
46. ticlopidine.tw
47. ticlid.tw
48. phosphodiesterase inhibitors.tw
49. cilostazol.tw
50. pletal.tw
51. glycoprotein IIB/IIIA inhibitors.tw
52. abciximab.tw
53. reoPro.tw
54. eptifibatide.tw
55. integrilin.tw
56. tirofiban.tw
57. aggrastat.tw
58. adenosine reuptake inhibitors.tw
59. dipyridamole.tw
60. persantine.tw
61. thromboxane synthase inhibitors.tw
62. thromboxane receptor antagonists.tw
63. terutroban.tw
64. acenocoumarol.tw
65. phenindione.tw
66. jantoven.tw
67. marevan.tw
68. lawarin.tw
69. waran.tw
70. warfant.tw

#### **Appendix 4. Data collection sheet**

The Study	
The year	
Patients studied	
Drug type	
Patients not on drug	
Patients on drug	
Recurrences not on drug	
Recurrences on drug	
Bilateral not on drug	
Bilateral on drug	
Unknown indication	
Time between the first operation and reoperation	
Time between the trauma and first operation	
Mortality	
Result	
Outcome	

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## Appendix 5. Modified table of bias

Risk of bias	Criterion	Comment
Selection bias	Were participants analyzed within the groups they were originally assigned to?	
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?	
	Did the strategy for recruiting participants into the study differ across study groups?	
	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?	
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	
	Did the study maintain fidelity to the intervention protocol?	
Attrition bias	If attrition (overall or differential nonresponse, dropout, loss to follow-up, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?	
Detection bias	Was the time period between the intervention/exposure and outcome the same for cases and controls?	
	Were the outcome assessors blinded to the intervention or exposure status of participants?	
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	
	Were outcomes assessed/defined using valid and reliable measures, implemented consistently across all study participants?	
	Were confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?	
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	